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| EXAMINER | |
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| GOON, SCARLETT Y | |
| **ART UNIT** | **PAPER NUMBER** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/579,620 | DEFREES ET AL. | |
| | Examiner | Art Unit | |
| | SCARLETT GOON | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *4-6,8-10,14,15,17-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 7, 11-13, 16 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *16 May 2006, 4 December 2008, 23 March 2009 and 3 June 2010*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-28 are pending in the instant application.

### *Election/Restrictions*

Applicants' election without traverse of Group I, claims 1-16 and 27, drawn to a granulocyte colony stimulating factor peptide, in the reply filed on 3 June 2010, is acknowledged.

In reply to a requirement for an election of a single disclosed species, Applicants further elected, without traverse, (i) branched poly(ethylene glycol residue; (ii) the species of $R^1$ having the structure as indicated in the response filed on 3 June 2010; and (iii) threonine as the amino acid. As Applicants did not elect a single disclosed species for the glycan structure, Ms. Christine Cochran, Applicants' attorney, was contacted on 24 June 2010 to request a telephone election. Ms. Cochran indicated on 28 June 2010 that Applicants elected for the glycan moiety as recited in claim 7.

Claims 17-26 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3 June 2010.

Claims 4-6, 8-10, 14 and 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3 June 2010.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-3, 7, 11-13, 16 and 27 will be examined on its merits herein.

***Priority***

This application is a continuation of U.S. application no. 10/411,037 filed on 9 April 2003, which is a continuation-in-part of U.S. application no. 10/360,779 filed on 19 February 2003, which is a continuation-in-part of U.S. application no. 10/360,770 filed on 6 January 2003, which is a continuation-in-part of U.S. application no. 10/287,994 filed on 5 November 2002, which is continuation of PCT/US02/32263 filed on 9 October 2002, which claims priority to U.S. provisional application no. 60/407,527 filed on 28 August 2002, U.S. provisional application no. 60/404,249 filed on 16 August 2002, U.S. provisional application no. 60/396,594 filed on 17 July 2002, U.S. provisional application no. 60/391,777 filed on 25 June 2002, U.S. provisional application no. 60/387,292 filed on 7 June 2002, U.S. provisional application no. 60/334,301 filed on 28 November 2001, U.S. provisional application no. 60/334,233 filed on 28 November 2001, U.S. provisional application no. 60/344,692 filed on 19 October 2001, and U.S. provisional application no. 60/328,523 filed on 10 October 2001.

Applicants' claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir 1994). Also see MPEP § 201.11.

The disclosure of the prior-filed applications fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior filed applications do not disclose a granulocyte colony stimulating factor peptide comprising the moiety as recited in claim 1. More particularly, the prior filed applications do not disclose a moiety of claim 1 which encompasses all of the limitations of G and $R^1$.

Thus, the priority date of the instant claims is deemed to be the filing date of the instantly filed application, 19 April 2007. If Applicants disagree, Applicants should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicants are reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

In clarifying the priority date of the instant claims, Applicants should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to said priority date.

***Information Disclosure Statement***

The information disclosure statements (IDS) dated 16 May 2006, 4 December 2008, 23 March 2009 and 3 June 2010 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, except where noted. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

Copeland, cited on the IDS dated 4 December 2008, was not considered because p. 148-149 was missing. Both Hermanson references were not considered because the citation did not list any page numbers, thereby suggesting the entire book was for consideration, but only the Table of Contents from the book were provided to the Office. Takeda *et al.* and Wang *et al.* were not considered because the scanned images were not readable. The article from Endocrine, vol. 11, p. 205-215 was not considered because of copy of the article was not provided to the Office. Furthermore, the citation does not list the year of publication for the article. The Haneda *et al.* citation has been amended to include the publication year of 1996.

Doc. No. HW and HX on the IDS dated 3 June 2010 were not considered because the citation did not list relevant pages and only the title page of the book was submitted to the Office. For consideration, relevant pages must be cited and copies of the pages must be provided to the Office. If Applicants deem the entire book to be relevant, a copy of the pages from the book must be provided. Doc. No. IY was corrected for incorrect citation of author.

In searching for the elected compound, the Examiner found art which reads on the glycan structures as recited in claims 8-10. In an effort to expedite prosecution, the Examiner has applied this art. This application, however, should not be construed as a withdrawal of the species election.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 7-13, 16 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 03/031464 to DeFrees *et al.* (IDS dated 3 June 2010), as evidenced by journal article publication by Oh-eda *et al.* (PTO-892, Ref. W).

DeFrees *et al.* disclose methods and compositions for remodeling a peptide molecule, including the addition or deletion of one or more glycosyl groups to the peptide, and/or the addition of a modifying group to the peptide. Modifying groups include water-soluble polymers, such as poly(ethylene glycol) (p. 152, lines 7-25). The use of poly(ethylene glycol) to derivatize peptide therapeutics has been demonstrated to reduce the immunogenicity of the peptides and prolong their clearance time from

circulation (p. 4, lines 3-9). The PEG moiety has been shown to be attached via a peptide amino acid residue (p. 4, lines 13-20) or an oxidized glycosyl residue of the peptide (p. 4, line 28 – p. 5). In one embodiment, a conjugate is formed between G-CSF and a modifying group, wherein the modifying group is covalently attached to the G-CSF peptide through an intact glycosyl linking group, and the G-CSF peptide comprises a glycosyl residue having a formula as indicated (p. 23, lines 8-23; p. 297, line 19 – p.298, line 2). The modifying group exemplified in the disclosure of DeFrees *et al.* is poly(ethylene glycol) molecules, such as those in formula 3 (p. 154, line 28 – p. 156). The PEG molecules disclosed on p. 156 meet the limitations of the $R^1$ structure of the instant claims. DeFrees *et al.* further disclose a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a covalent conjugate between a polymer and a glycosylated or non-glycosylated peptide, wherein the polymer is conjugated to the peptide via an intact glycosyl linking group interposed between and covalently linked to both the peptide and the polymer (p. 21, lines 9-12). Scheme 3 discloses a modified glycoPEG-ylated compound, such as albumin-PEG-SA-EPO, wherein EPO represents erythropoietin and SA represents sialic acid, which can be used in a method for extending the blood-circulation half-life of selected peptides (p. 149, Scheme 3 and lines 1-10). Formula 1 discloses the structure of a remodeled N-linked glycan, comprising a tri-mannosyl core, preferably linked to an asparagine residue on a peptide backbone (p. 129, lines 10-21). Figure 9 depicts well-known strategies for the synthesis of biantennary, triantennary and even tetraantennary glycan structures beginning with the trimannosyl core structure. Methods for the modification

of O-linked glycans wherein the peptide is modified with a GalNAc donor, followed by Gal and SA via the use of appropriate glycosyltransferases is also disclosed (p. 140, lines 20-28). The remodeled peptide has the structure as shown in Formula (2), wherein $X^2$ is a sialic acid residue and f = 0 or 1 (p. 137, line 2 – p. 138, line 14). The modifying group can be attached to sialic acid at either the 9-position on the pyruvyl side chain or at the 5-position on the amine moiety of sialic acid (p. 150, lines 5-11). The preparation of CMP-SA-PEG, wherein PEG is attached to the C5 position, is disclosed in Scheme 4 (p. 177) and further exemplified in Example 8 (p. 348, line 4 – p. 351, line 21). Table 2 also discloses CMP-SA compounds wherein the glycerol side chain is modified with PEG, such as on the 9-position (p. 178). Preparation of the 9-modified CMP-SA compound is disclosed in Scheme 8 (p. 181). Figure 27 provides a schematic representation for the modification of glycan structures on G-CSF with PEG (p. 83, lines 9-14). Additionally, Figure 27A shows that G-CSF has one site for O-linked glycosylation, occurring at position 133 of the peptide backbone. Figure 52 discloses exemplary nucleotide and corresponding amino acid sequences of G-CSF as SEQ ID Nos 1 and 2, respectively (p. 92, lines 1-3). SEQ ID No. 1 of DeFrees *et al.* has the same sequence as SEQ ID No. 1 of the instant application. Figure 126 discloses the results of an *in vitro* bioassay comparing PEGylated EPO with non-PEGylated EPO (p. 99, lines 22-25). EPO glycoPEGylated with 1 kDa PEG had almost the same activity as the unglycoPEGylated EPO when both were at a concentration of approximately 5 μg/mL. The EPO glycoPEGylated with 10 kDa PEG had approximately half the activity

of the unglycoPEGylated EPO when both were at a concentration of approximately 5 μg/mL (p. 363, line 30 - p. 364, line 4).

It is noted that DeFrees *et al.* is silent regarding the glycosylated amino acid and the structure of glycans present on G-CSF. However, as evidenced by Oh-eda *et al.*, *O*-glycoslyation occurs at Thr-133 in hG-CSF, and has the structure NeuAcα2-3Galβ1-3(±NeuAcα2-6)GalNAcol (column 2, first incomplete paragraph).

It is further noted that DeFrees *et al.* do not expressly teach that PEGylated EPO is tissue protective or essentially non-erythropoietically active, as recited in the instant claims. However, the recitations "is essentially non-erythropoietically active" and "is tissue protective" are considered to be a result of the structural claim limitations. Thus, Applicants' recitations are not considered to further limit the claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount, as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See also MPEP § 2112.01.

Thus, the disclosure of a glycoPEGylated G-CSF, as well as methods for the preparation of said structure, disclosed by DeFrees *et al.*, anticipates claims 1, 2, 7-13, 16 and 27.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Section [0001]**

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 03/031464 to DeFrees *et al.* (IDS dated 3 June 2010), as evidenced by journal article publication by Oh-eda *et al.* (PTO-892, Ref. W), as applied to claims 1, 2, 7-13, 16 and 27, further in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; IDS dated 3 June 2010), in view of journal article publication by Felix *et al.* (IDS dated 3 June 2010), in view of WO 99/55376 A1 to El-Tayar *et al.* (PTO-892, Ref. N).

The teachings of DeFrees *et al.* were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of DeFrees *et al.* differ from that of the instantly claimed invention in that DeFrees *et al.* do not disclose the specific branched PEG structures as recited in the instant claims.

The Martinez '575 patent teaches branched, non-antigenic polymers and conjugation of the polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life *in vivo*. One of the chief advantages for the use of branching polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with (column 2, lines 42-51). Another advantage is that the branched polymers provide the benefits associated with attaching several strands of polymers to a bioeffecting material, but require substantially fewer conjugation sites, which is apparent in therapeutic agents having few available attachment sites (column 2, lines 52-59). The branched polymers are represented by formula (I), $(R)_nL$-A, wherein R is the water-

soluble polymer, n is 2 or 3, L is the aliphatic linking moiety covalently lined to R, and A represents the activating functional group (column 3, lines 11-22). The polymers are preferably prepared from methoxypoly (ethylene glycols), or other suitable alkyl substituted poly(alkylene oxide) derivative, such as those containing mono or bis terminal $C_1$-$C_4$ groups (column 2, lines 65 - column 3, line 4). Straight-chained non-antigenic polymers such as monomethyl PEG (mPEG) homopolymers are preferred (column 3, lines 4-6). It is preferred that each mPEG chain have a molecular weight of between 200 and about 12,000 Da, with molecular weights of about 5,000 Da being most preferred (column 3, lines 23-29). The variable L preferably includes a multiply-functionalized alkyl group containing up to 13, and more preferably, between 1-10 carbon atoms (column 3, lines 59-63). A heteroatom, such as nitrogen, oxygen or sulfur may be included within the alkyl chain, which may also be branched at a carbon or nitrogen atom. The variable “A” is selected from any functional group that is capable of reacting with 1) an amino group, 2) a carboxylic acid group or reactive carbonyl group, or 3) mercapto or sulfhydryl groups. The variable “A” can also include a spacer moiety located proximal to the aliphatic linking moiety “L” (column 4, lines 47-50). Biologically active molecules of interest include, but are not limited to, proteins, peptides, polypeptides, enzymes, organic molecules of natural and synthetic origin such as medicinal chemicals, and the like (column 7, lines 40-45). Among the list of proteins cited as being of interest are cytokines, such as interleukins, alpha-, beta-, and gamma-interferons and granulocyte colony stimulating factor (column 7, lines 57-64). Example

8 discloses the preparation of a branched PEG structure wherein lysine is the linker conjugated to two linear mPEG compounds (column 13, lines 20-40).

Felix *et al.* teach the synthesis of symmetrically and asymmetrically branched pegylating reagents. PEG-protein conjugates have been shown to have improved bioavailability and therapeutic efficacy stemming from increased resistance to proteolytic degradation, enhanced pharmacokinetic and improved pharmacodynamic properties, and reduced renal clearance (p. 86, column 1, first paragraph). Additionally, many pegylated proteins have been reported to have increased plasma half-lives and reduced antigenicity and immunogenicity (p. 86, column 1, first paragraph). Branched PEGs offer an additional dimension of steric protection to the proteins to which they are linked (p. 86, column 2, bridging paragraph). Lysine has been used successfully as a spacer for branched PEG structures (p. 86, column 1, last paragraph). It is expected that introduction of additional branches to PEG would provide additional levels of enzymatic protection to the proteins to which they are linked (p. 86, column 2, first full paragraph). Felix *et al.* disclose a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the linker (p. 87, column 1, Figure 1). Methods for the preparation of the bis-pegylating reagent and tris-pegylating reagent are disclosed in Figure 2 (p. 87).

El-Tayar *et al.* teach PEG-LHRH analog conjugates, where a PEG moiety is covalently bound to a serine residue of a LHRH analog either directly or via a bifunctional linker molecule, such as an amino acid (p. 4, last paragraph). El-Tayar *et*

*al.* teach that branched PEGs are in common use (p. 1, last paragraph). El-Tayar *et al.* disclose serine as one such amino acid bifunctional linker (p. 8).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of DeFrees *et al.*, concerning methods for the preparation of glycosylated G-CSF, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, e.g. G-CSF, as a means to extend their circulating half-life *in vivo*, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids as the backbone linker, with the teachings of El-Tayar *et al.*, regarding the use of amino acids as bifunctional linkers.

Since both the Martinez '575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to use the branched PEG polymers disclosed in the Martinez '575 patent, or by Felix *et al.*, with hydrazide reactive groups for conjugation to glycans present on the peptide, such as that disclosed by Wright, in order to receive the expected benefit that the resulting branched PEGylated G-CSF would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since the Martinez '575 patent teaches that branched PEG polymers can be synthesized by using any linker that comprises a multiply-

functionalized alkyl group containing up to 13 carbons, further exemplifying lysine as such a linker, and Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine. Furthermore, since the teachings of El-Tayar *et al.* show that the use of amino acids, such as serine, as bifunctional linkers are known, one of ordinary skill in the art would have a reasonable expectation of success that such a substitution would similarly generate useful branched PEG polymers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

**Section [0002]**

Claims 1, 2, 7-13, 16 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0605963 A2 to Wright (IDS dated 4 December 2008), as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; IDS dated 3 June 2010), in view of U.S. Patent No. 5,824,778 to

Ishikawa *et al.* (hereinafter referred to as the '778 patent; IDS dated 3 June 2010), in view of PG Pub No. US 2002/0016003 to Saxon *et al.* (IDS dated 3 June 2010), in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; IDS dated 3 June 2010), in view of journal article publication by Monaco *et al.* (PTO-892, Ref. U), as evidenced by Nagata *et al.* (PTO-892, Ref. V), as evidenced by journal article publication by Oh-eda *et al.* (PTO-892, Ref. W).

Wright teaches methods and compounds for modifying polypeptides with PEG or other water-soluble organic polymers. Protein and other similar organic molecules are chemically modified by covalent conjugation to water-soluble organic polymers, such as PEG, because of the desirable properties conferred on the polypeptides by attachment of the water-soluble polymers. The desirable properties include solubility in aqueous solutions, increased stability during storage, reduced immunogenicity, increased resistance to enzymatic degradation, compatibility with a wider variety of drug administration systems, and increased *in vivo* half-life (p. 2, lines 11-16). Conjugation of mPEG to a cysteine residue of EPO is known (p. 3, lines 5-9). However, Wright teaches that it may be advantageous to couple water-soluble reagents to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins (p. 3, lines 38-46). By providing for water-soluble polymer reagents that may be coupled to the carbohydrate moiety of glycoproteins it may be possible to covalently conjugate

water-soluble polymers to proteins without substantially adversely affecting the biological activity of proteins that would be adversely affected through coupling at other amino acid residues (p. 3, lines 47-50). Wright teaches that hydrazine and oxylamine derivatives of water-soluble polymers, such as PEG, may be covalently attached to proteins through reactions with aldehyde groups or other suitable functional groups present on the protein of interest (p. 7, lines 5-11). Aldehyde groups may be introduced by partially oxidizing the hydroxyl groups on the polypeptide, such as hydroxyl groups present on the carbohydrate moieties of the polypeptide, with galactose oxidase or periodate (p. 7, lines 11-16). Hydrazide and oxylamine derivatives are further disclosed (p. 7, lines 19-58). Examples of PEG water soluble polymers include polyethylene glycol, methoxypolyethylene glycol, polyethylene glycol homopolymers, polypropylene glycol homopolymers, copolymers of ethylene glycol with propylene glycol (p. 7, line 58 – p. 8, line 3). Wright further teaches that the disclosed preparation may be administered alone or in an admixture with a pharmaceutical carrier or diluent selected with regard to the intended route of administration and standard pharmaceutical practice (p. 12, lines 14-21). Polypeptides of interest for water-soluble polymer derivatization include hormones, lymphokines, cytokines, growth factors, enzymes, vaccine antigens, and antibodies (p. 4, lines 26-29). Methods for the synthesis of mPEG-hydrazide from mPEG-OH (p. 12, line 55 - p. 13, line 37) and mPEG-semicarbazide from mPEG-$NH_2$ (p. 13, line 50 – p. 14, line 16) are further disclosed. Methods for the modification of a peptide with mPEG-hydrazide and mPEG-semicarbazide are further exemplified with EPO, wherein EPO is oxidized with sodium periodate followed by conjugation of the

resulting aldehyde to PEG (p. 18, line 26 - p. 19, line 14). It is noted that Wright does not expressly teach which carbohydrate group is oxidized to an aldehyde in the presence of sodium periodate. However, as evidenced by Kinstler *et al.*, 10 mM sodium periodate oxidation of EPO targets the pendant diol of the penultimate glycosyl unit sialic aicd residue (p. 11, lines 1-10 and p. 19, lines 29-33).

Although Wright expressly disclose cytokines as polypeptides that would be useful when conjugated to water-soluble polymers, such as PEG, Wright does not expressly disclose specific cytokines, such as granulocyte colony stimulating factor, as recited in the instant claims.

The Ishikawa '778 patent discloses a polyethylene glycol-modified human granulocyte colony stimulating factor (G-CSF). The polyethylene glycol (PEG) is covalently bound through amino acid residues of the polypeptide of human G-CSF, such as those having a free amino group (e.g. lysine and the N-terminal amino acid residue) and those having the free carboxyl group (e.g. aspartic acid, glutamic acid and the C-terminal amino acid residue) (column 2, line 66 – column 3, line 8). The PEG modified human G-CSF has a more enduring pharmacological effect, which may be possibly attributed to its prolonged half-life in the body (column 4, lines 16-18). The PEG modified human G-CSF has essentially the same biological activity as an intact human G-CSF and is therefore useful in the treatment of general haematopoietic disorders, including those arising from chemotherapy or from radiation therapy (column 4, lines 22-31). The PEG modified human G-CSF may be formulated into pharmaceuticals containing also a pharmaceutically acceptable diluent, an agent for

preparing an isotonic solution, a pH-conditioner, and the like, in order to administer them into a patient (column 4, lines 32-36).

Saxon *et al.* teach a method for covalent modification of molecules. The chemoselective ligation reaction can be carried out under physiological conditions, and involves condensation of a specifically engineered phosphine, which can provide for formation of an amide bond between the two reactive partners resulting in a final product comprising a phosphine oxide, or which can be engineered to comprise a cleavable linker so that a substituent of the phosphine is transferred to the azide of the other molecule (paragraph 0018). The selectivity of the reaction and its compatibility with aqueous environments provides for its application *in vivo* and *in vitro*, e.g. synthesis of peptides and other polymers. Saxon *et al.* disclose the use of a synthetic substrate comprising an abiotic reactive partner, such as the azido compounds of paragraphs 0067-0070, for incorporation into a biopolymer, which is utilized in the glycoprotein biosynthetic pathway. For example, host cells provided with synthetic sialic acid azido-derivatives, such as those disclosed in paragraphs 0067-0070, incorporate these compounds into the sialic acid biosynthetic pathway, eventually resulting in the incorporation and expression of the synthetic sugar residues on glycoproteins (paragraph 0066). The azido-modified glycoprotein can then undergo a chemoselective ligation reaction with another molecule engineered with a phosphine. The engineered phosphine can be modified to comprise a molecule desired for delivery and conjugation to the azido-target substrate, such as that comprising detectable labels, small molecule drugs, cytotoxic molecules, ligands for binding by a target receptor, tags to aid in

purification, and molecules to facilitate selective attachment of the polypeptide to a surface (paragraph 0075). The chemoselective ligation can be performed with a modified phosphine that comprises a cleavable linker. Thus, reaction of i) a first reactant comprising a first molecule of interest engineered with a phosphine comprising a cleavable linker, with ii) a second reactant comprising a second molecule of interest engineered with an azide, results in conjugation of the first molecule of interest to the second molecule of interest via an amide or a thioamide bond, accompanied by the release of nitrogen and an oxidized phosphine byproduct (paragraph 0109). This reaction is further schematically illustrated in paragraph 0109. As shown in Example 6, cells incorporate N-azidoacetylmannosamine into cell surface glycans, as detected by labeling of the cells with biotin modified with a phosphine group, followed by FITC-avidin staining (paragraph 0198). Example 7 illustrates a method wherein two peptides, one modified with an azido group, and the other modified with a phosphine group with a cleavable linker, are conjugated together to form an amide bond between the two peptides. Saxon *et al.* further disclose that previous work showed that incorporation of a ketone-bearing group, such as a levulinoyl group, can be expressed on glycoproteins as SiaLev, wherein the levulinoyl group is present at the 5-position of sialic acid, and that the ketone group on SiaLev can be chemoselectively conjugated to compounds or other molecules bearing a hydrazide group (paragraphs 0008-0010).

The teachings of the Martinez ‘575 patent were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

Monaco *et al.* teach a method for expression of recombinant human granulocyte colony-stimulating factor in CHO dhfr$^-$ cells. The system yields a larger proportion of clones producing high amounts of recombinant protein, as compared to clones from the classical co-transfection protocol (p. 149, subheading "Conclusions"). The G-CSF sequence is that same as the sequence published by Nagata *et al.* As evidenced by Nagata *et al.*, the human G-CSF sequence of Monaco *et al.* is the same as SEQ ID No. 1 of the instant application. Furthermore, it is noted that Monaco *et al.* is silent regarding the site of glycosylation, and the structure of glycosyl residues, on the HG-CSF polypeptide backbone in CHO cells. As evidenced by Oh-eda *et al.*, *O*-glycoslyation occurs at Thr-133 in hG-CSF, and has the structure NeuAc$\alpha$2-3Gal$\beta$1-3(±NeuAc$\alpha$2-6)GalNAcol (column 2, first incomplete paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Wright, concerning the modification of peptides, such as cytokines, with water-soluble polymers, such as PEG, with the teachings of the Ishikawa '778 patent, concerning conjugation of PEG to human G-CSF via the amino acids of the polypeptide to increase its half-life in the body, with the teachings of Saxon *et al.*, regarding chemoselective ligations involving a ketone group with a hydrazide group, or an azido group with a phosphine, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, e.g. FSH, as a means to extend their circulating half-life *in vivo*, with the teachings of Monaco *et al.*, regarding the cloning and expression of recombinant human granulocyte colony-stimulating factor

in CHO cells. Since Wright teaches that polypeptides, such as cytokines, are advantageously conjugated to PEG polymers through the glycosylations present on those peptide molecules rather than to the amino acids of the polypeptide backbone because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins, and the Ishikawa '778 patent teaches that conjugation of PEG to human G-CSF via the amino acids of the polypeptide increases its half-life in the body, one of ordinary skill in the art would have been motivated to substitute the conjugation method of the Ishikawa '778 patent with that disclosed by Wright, with the reasonable expectation that it would also yield a PEG conjugated human G-CSF polypeptide with increased half-life in the body. Furthermore, as Wright teaches that conjugation of polypeptides to PEG reduces the immunogenicity of biologically active macromolecules or increases their *in vivo* half-life, while maintaining their activity, and the Martinez '575 patent teaches that branched, non-antigenic polymers can be conjugated to biologically active molecules, such as cytokines, as a means to extend their circulating half-life *in vivo*, it would have been *prima facie* obvious for one of ordinary skill in the art to conjugate PEG to human G-CSF via the glycosylations present on the macromolecules, as described by Wright. Since both Wright and the Martinez '575 patent teach conjugation of PEG to biological macromolecules as a means to extend their serum half-life, and Wright further teaches that cytokines can be conjugated using their disclosed method, one of ordinary skill in the art would reasonably expect that the use of human G-CSF, as disclosed in the

Martinez '575 patent, for conjugation to a PEG polymer using the method disclosed by Wright, would result in PEGylation of G-CSF at the glycosyl moiety present on G-CSF.

Furthermore, as Wright teaches that PEG-hydrazide polymers are conjugated to the carbohydrate moiety of biological macromolecules by oxidizing the carbohydrate moiety to an aldehyde or other suitable functional group, one of ordinary skill in the art would have been motivated to conjugate these same PEG-hydrazide derivative onto the carbohydrate residue of glycoproteins expressing a ketone group, such as that present on SiaLev, as disclosed by Saxon *et al.* Since Saxon *et al.* teach that biotin-hydrazide can be selectively conjugated to the ketone group of SiaLev, which is expressed on the terminus carbohydrate residue of a glycoprotein, one of ordinary skill in the art would reasonably expect that substitution of biotin-hydrazide with PEG-hydrazide would yield a predictable result. One of ordinary skill in the art would consider this to be an advantageous method because it eliminates the need for an oxidation step on the carbohydrate residue.

With regards to obtaining G-CSF containing a terminal SiaLev group on its glycans, Monaco *et al.* teach the expression of rhG-CSF in a CHO system. Thus, based on the combined teachings of Saxon *et al.* and Monaco *et al.*, one of ordinary skill in the art would reasonably expect that expression of G-CSF in the CHO system in the presence of a mannosamine compound as disclosed by Saxon *et al.*, would predictably yield G-CSF modified with SiaLev on the terminus of its glycans. Moreover, as Saxon *et al.* teach that azido groups can be introduced onto sialic acids present on glycoproteins using a similar method to that of SiaLev, and that the azido groups

chemoselectively react with phosphine groups, one of ordinary skill in the art would have been motivated to alternately modify the PEG-hydrazide compounds, disclosed by Wright, into PEG-phosphine compounds for conjugation to azido groups introduced onto the sialic acid residue of glycoproteins. One of ordinary skill in the art would have been motivated to select the azide-phosphine chemistry, in order to receive the expected benefit, as disclosed by Saxon *et al.*, that these two groups are abiotic to cell surfaces. One of ordinary skill in the art would have been motivated to conjugate PEG onto G-CSF, in order to receive the expected benefit, as disclosed by Wright, that conjugation of PEG to a peptide increases its solubility in aqueous solutions, stability during storage, and resistance to enzymatic degradation, and reduces its immunogenicity, as well as increasing its *in vivo* half-life. Moreover, as disclosed by Wright, it may be advantageous to couple PEG to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins. Thus, although Saxon *et al.* exemplify conjugation of a hydrazide or phosphine group onto sialic acid derivatives expressed on glycoproteins as a detection method, Saxon *et al.* do disclose that small molecules, peptide, ligands, etc., could be conjugated to the azido or ketone group introduced onto sialic acid. As such, in view of the teachings of Wright, it would have been *prima facie* obvious to one of ordinary skill in the art that other molecules, such as PEG-hydrazide or PEG-phosphine, could be conjugated to the sialic acid derivatives present on the glycoproteins.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

**Section [0003]**

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0605963 A2 to Wright (IDS dated 4 December 2008), as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; IDS dated 3 June 2010), in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.* (hereinafter referred to as the '778 patent; IDS dated 3 June 2010), in view of PG Pub No. US 2002/0016003 to Saxon *et al.* (IDS dated 3 June 2010), in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; IDS dated 3 June 2010), in view of journal article publication by Monaco *et al.* (PTO-892, Ref. U), as evidenced by Nagata *et al.* (PTO-892, Ref. V), as evidenced by journal article publication by Oh-eda *et al.* (PTO-892, Ref. W), as applied to claims 1, 2, 7-13, 16 and 27, further in view of journal article publication by Felix *et al.* (IDS dated), in view of WO 99/55376 A1 to El-Tayar *et al.* (PTO-892, Ref. N).

The combined teachings of Wright, the Ishikawa '778 patent, Saxon *et al.*, the Martinez '575 patent, and Monaco *et al.*, as evidenced by the Kinstler '398 patent, Nagata *et al.*, and Oh-eda *et al.*, were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of the prior art differ from that of the instantly claimed invention in that the prior art references do not disclose the specific branched PEG structures as recited in the instant claims.

The teachings of the Felix *et al.* and El-Tayar were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Wright, concerning the modification of peptides, such as cytokines, with water-soluble polymers, such as PEG, with the teachings of the Ishikawa '778 patent, concerning conjugation of PEG to human G-CSF via the amino acids of the polypeptide to increase its half-life in the body, with the teachings of Saxon *et al.*, regarding chemoselective ligations involving a ketone group with a hydrazide group, or an azido group with a phosphine, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, e.g. G-CSF, as a means to extend their circulating half-life *in vivo*, with the teachings of Monaco *et al.*, regarding the cloning and expression of recombinant human granulocyte colony-stimulating factor in CHO cells, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids as the backbone linker, with the teachings of El-Tayar *et al.*, regarding the use of amino acids as bifunctional linkers.

Since both the Martinez '575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an

umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to modify the branched PEG polymers disclosed in the Martinez '575 patent, or by Felix *et al.*, with hydrazide reactive groups for conjugation to glycans present on the peptide, such as that disclosed by Wright, in order to receive the expected benefit that the resulting branched PEGylated G-CSF would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since the Martinez '575 patent teaches that branched PEG polymers can be synthesized by using any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, further exemplifying lysine as such a linker, and Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine. Furthermore, since the teachings of El-Tayar *et al.* show that the use of amino acids, such as serine, as bifunctional linkers are known, one of ordinary skill in the art would have a

reasonable expectation of success that such a substitution would similarly generate useful branched PEG polymers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Section [0001]**

Claims 1, 2, 7, 8, 16 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 7,138,371 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a covalent conjugate between a peptide and poly(ethylene glycol), wherein said poly(ethylene glycol) is covalently attached to said peptide at a glycosyl or amino acid residue of said peptide via an intact glycosyl linking group comprising a sialic acid residue covalently linked to said poly(ethylene

glycol), wherein said sialic acid residue is covalently attached to said glycosyl or amino acid residue of said peptide by reaction between said peptide and a modified sugar donor comprising sialic acid covalently linked to said poly(ethylene glycol), and wherein said reaction is catalyzed by a sialyltransferase. The structure of the glycosyl moiety is as disclosed in claim 11. The peptide is selected from a group that includes granulocyte-colony stimulating factor peptide (claims 14, 19, 25, 28).

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 7, 8, 16 and 27 are seen to be anticipated by claims 1-30 of U.S. Patent No. 7,138,371 B2.

**Section [0002]**

Claims 1, 2, 7-9, 16 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-103 of U.S. Patent No. 7,173,003 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a cell-free, in vitro method of forming a

covalent conjugate of a G-CSF peptide, said peptide having the formula as recited in the claims. The glycosyltransferase is ST3Gal3, and the modified sialic acid structure is as disclosed in claim 72.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 7-9, 16 and 27 are seen to be anticipated by claims 1-103 of U.S. Patent No. 7,173,003 B2.

**Section [0003]**

Claims 1, 2, 7-9, 16 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-120 of U.S. Patent No. 7,416,858 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a covalent conjugate between a poly(ethylene glycol) and a glycosylated or non-glycosylated peptide, wherein said poly(ethylene glycol) is conjugated to said peptide via a glycosyl linking group wherein

said glycosyl linking group is interposed between and covalently linked to both said peptide and said poly(ethylene glycol). The polyalkylene oxide is poly(ethylene glycol). The structure of the glycosyl moiety is as disclosed in claims 24, 25, 28, 30, 41, 51, 60 and 112. The peptide is selected from a group that includes granulocyte-colony stimulating factor peptide (claims 9, 23, 40, 50, 59, 72, 101, 111 and 120).

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 7-9, 16 and 27 are seen to be anticipated by claims 1-120 of U.S. Patent No. 7,416,858 B2.

**Section [0004]**

Claims 1, 2, 16 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-43 of U.S. Patent No. 7,473,680 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of forming a covalent conjugate between a water soluble polymer and a glycosylated or non-glycosylated

peptide, wherein said water soluble polymer is conjugated to said peptide via an intact glycosyl linking group interposed between and covalently linked to both said peptide and said water soluble polymer. Claims 41 and 43 indicate that the peptide is selected from a group that includes G-CSF peptide.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 41-43 of U.S. Patent No. 7,473,680 B2.

**Section [0005]**

Claims 1, 2, 16 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 7,691,603 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of forming a peptide comprising a covalent linkage between a glycosylated or non-glycosylated peptide, wherein said modifying group is conjugated to the peptide via glycosyl linking group

interposed between and covalently linked to both said peptide and said modifying group. At least one modifying group is a water-soluble polymer. Claim 9 indicates that the water soluble polymer that comprises PEG. Claim 13 indicates that the peptide is selected from a group that includes G-CSF peptide.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 1-17 of U.S. Patent No. 7,691,603 B2.

**Section [0006]**

Claims 1-3, 7-13, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 215-245 of copending U.S. application no. 11/652,467.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a granulocyte-colony stimulating factor peptide conjugate comprising a modifying group wherein the modifying group is covalently attached to the peptide at an amino acid of the peptide via

an intact glycosyl linking group. The peptide is glycosylated at a threonine residue. The glycosyl residue has the formula as indicated in claim 216. The modifying group is a water soluble polymer selected from the group consisting of peptides, saccharides, poly(ethers), poly(amines and poly(carboxylic acids). The water soluble polymer comprises polyethethylene glycol. The claims of the instant application are also drawn to a composition comprising the granulocyte-colony stimulating factor peptide conjugate.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1-3, 7-13, 16 and 27 are seen to be anticipated by claims 215-245 of copending U.S. application no. 11/652,467.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0007]**

Claims 1, 2, 10, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 50-62 of copending U.S. application no. 10/585,385.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a pharmaceutical composition comprising a granulocyte colony stimulating factor comprising an effective amount of the G-CSF polypeptide mutant wherein said polypeptide is glyconjugated with a modified sugar. The modified sugar is modified with a member selected from poly(ethylene glycol) and mPEG. The copending application is also drawn to a method of providing G-CSF therapy to a subject in need thereof, a method of providing interferon therapy to a subject in need thereof, and a method of providing growth hormone therapy to a subject in need therof, comprising administering the claimed granulocyte colony stimulating factor peptide conjugate.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 10, 16 and 27 are seen to be anticipated by claims 50-62 of copending U.S. application no. 10/585,385.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0008]**

Claims 1-3, 7, 8 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of copending U.S. application no. 11/166,404.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a granulocyte colony stimulating factor conjugate comprising a glycosyl linking group attached to an amino acid residue of said peptide, said glycosyl linking group comprising a modified sialic acid residue having the formula as indicated in claims 1 and 21, and a pharmaceutical composition comprising the said granulocyte colony stimulating factor conjugate. The structures of the glycosyl residue are as shown in claims 4, 10, 11, 14, 24, 25 and 35. The copending application is also drawn to a method of stimulating inflammatory leukocyte production in a mammal, and a method of treating infection in a subject in need thereof, comprising administering the claimed granulocyte colony stimulating factor peptide conjugate.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9.

The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1-3, 7, 8 16 and 27 are seen to be anticipated by claims 1-41 of copending U.S. application no. 11/166,404.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0009]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-23 of copending U.S. application no. 11/597,258.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of catalyzing the transfer of a sialic acid moiety to an acceptor moiety comprising incubating a ST6GalNAcI polypeptide with a CMP-NAN sialic acid donor and a polypeptide acceptor, wherein said polypeptide acceptor is selected from a group that includes granulocyte colony stimulating factor. The sialic acid moiety comprises a polyethylene glycol moiety.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene

glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 20-23 of copending U.S. application no. 11/597,258.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0010]**

Claims 1, 2, 11, 13, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending U.S. application no. 11/794,560.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a granulocyte colony stimulating factor peptide comprising a glycosyl linking group attached to an amino acid residue of said peptide, said glycosyl linking group comprising a modified sialic acid residue having the formula as indicated in claims 1 and 21, and a pharmaceutical formulation comprising the said granulocyte colony stimulating factor conjugate. The modified sialic acid residue comprises PEG. The structures of the glycosyl residue are as shown in claims 6, 11, 14, 25 and 27. The copending application is also drawn to a method of stimulating inflammatory leukocyte production in a mammal, and a method of

treating infection in a subject in need thereof, comprising administering the claimed granulocyte colony stimulating factor peptide conjugate.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 11, 13, 16 and 27 are seen to be anticipated by claims 1-42 of copending U.S. application no. 11/794,560.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0011]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 17-32, 37-49, 71-74, 77-81, 83 and 84 of copending U.S. application no. 11/866,969.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of making a composition comprising a first polypeptide conjugate, said first polypeptide conjugate comprising a first number of poly(alkylene oxide) moieties covalently linked to said first

polypeptide. The poly(alkylene oxide) moieties are optionally linked to the glycan residue of the polypeptide (claim 4). The poly(alkylene oxide) moieties are selected from poly(ethylene glycol) and poly(propylene glycol) (claim 9). The copending application is also drawn to a composition comprising a first polypeptide conjugate, said first polypeptide conjugate comprising a first number of poly(alkylene oxide) moieties, each of said poly(alkylene oxide) moieties covalently linked to said first polypeptide via an intact glycosyl linking group. The first polypeptide is selected from a group that includes granulocyte colony stimulating factor (claims 12 32, 71 and 73). The claims of the copending application are also drawn to various methods of treatment comprising administering the composition to a subject in need thereof.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 1-12, 17-32, 37-49, 71-74, 77-81, 83 and 84 of copending U.S. application no. 11/866,969.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0012]**

Claims 1, 2 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending U.S. application no. 11/867,553.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a peptide conjugate comprising a peptide which is covalently attached to a moiety which is a member selected from that as shown in claim 1. As shown in claim 3, the moiety encompasses polyethylene glycol. The peptide is selected from a group that includes granulocyte colony stimulating factor (claim 4).

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2 and 16 are seen to be anticipated by claims 1-4 of copending U.S. application no. 11/867,553.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0013]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending U.S. application no. 12/152,587.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate comprising a structure according to Formula (I), and a composition comprising the polypeptide conjugate. The polypeptide is selected from a group that includes granulocyte colony stimulating factor (claim 2). The Z* glycosyl residue is selected from mannose, galactose, GalNAc, GlcNAc, Xyl, Glc, and sialic acid (claim 13). The modified glycan includes PEG (claim 18). The copending application is also drawn to a method of making the polypeptide conjugation of Formula (I).

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 1-20 of copending U.S. application no. 12/152,587.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0014]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 86-88 of copending U.S. application no. 12/418,530.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of making a composition comprising a first polypeptide conjugate, said first polypeptide conjugate comprising a first number of poly(alkylene oxide) moieties covalently linked to said first polypeptide. The poly(alkylene oxide) moieties are covalently linked to said first polypeptide via an N-linked glycan (claim 88). The first polypeptide is selected from a group that includes granulocyte colony stimulating factor (claims 86).

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 86-88 of copending U.S. application no. 12/418,530.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0015]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending U.S. application no. 12/443,428.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to peptide conjugate comprising a peptide which is covalently attached to a moiety which is a member selected from that as shown in claim 1. As shown in claim 3, the moiety encompasses polyethylene glycol. The peptide is selected from a group that includes granulocyte colony stimulating factor (claim 4).

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 1-4 of copending U.S. application no. 12/443,428.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0016]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending U.S. application no. 12/496,595.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a covalent conjugate between a peptide and a water-soluble polymer, wherein said water-soluble polymer is not a naturally occurring sugar and is covalently attached to said peptide through an intact glycosyl linking group, as well as a composition comprising the covalent conjugate. The water soluble polymer is a PEG (claim 3). The peptide is selected from a group that includes granulocyte colony stimulating factor (claim 14). The copending application is also drawn to a method of forming a covalent conjugate between a peptide and a water-soluble polymer.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9.

The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 1-20 of copending U.S. application no. 12/496,595.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Section [0017]**

Claims 1, 2, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 and 35-49 of copending U.S. application no. 12/663,056.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a covalent conjugate between a non-naturally occurring polypeptide and a polymeric modifying group, said non-naturally occurring polypeptide corresponding to a parent-polypeptide and comprising an exogenous O-linked glycosylation sequence that is not present, or not present at the same position, in said parent polypeptide, said O-linked glycosylation sequence being a substrate for a GlcNAc-transferase, and comprising an amino acid residue having a hydroxyl group, wherein said polymeric modifying is covalently linked to said polypeptide at said hydroxyl group of said O-linked glycosylation sequence via a glycosyl linking group. The polymeric modifying group is a water-soluble polymer (claim

5) selected from poly(alkylene oxide), dextran and polysialic acid (claim 6). The poly(alkylene oxide) is selected from PEG or mPEG (claims 7 and 8). The parent-polypeptide is selected from a group that includes granulocyte colony stimulating factor (claim 11). The copending application is also drawn to a composition comprising the covalent conjugate, and a method of forming a covalent conjugate between a polypeptide and a polymeric modifying group.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units (claim 3). The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 16 and 27 are seen to be anticipated by claims 1-23 and 35-49 of copending U.S. application no. 12/663,056.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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